Brain Positron Emission Tomography (PET) in Chronic Fatigue Syndrome: Preliminary Data

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Chronic fatigue syndrome (CFS) has been widely studied by neuroimaging techniques in recent years with conflicting results. In particular, using single-photon emission computed tomography (SPECT) and perfusion tracers, hypoperfusion has been found in several brain regions, although the findings vary across research centers. The objective of this study was to investigate brain metabolism of patients affected by CFS, using [^{18}F]fluorine-deoxyglucose (^{18}FDG) positron emission tomography (PET). We performed ^{18}FDG PET in 18 patients who fulfilled the criteria of the working case definition of CFS. Twelve of the 18 patients were females; the mean age was 34 ± 15 years (range, 15–68) and the median time from CFS diagnosis was 16 months (range, 9–138). Psychiatric diseases and anxiety/neurosis were excluded in all CFS patients. CFS patients were compared with a group of 6 patients affected by depression (according to DSM IV-R) and 6 age-matched healthy controls. The CFS patients were not taking any medication at the time of PET, and depressed patients were drug-free for at least 1 week before the PET examination. The PET images examined 22 cortical and subcortical areas. CFS patients showed a significant hypometabolism in right mediofrontal cortex ($P = 0.010$) and brainstem ($P = 0.013$) in comparison with the healthy controls. Moreover, comparing patients affected by CFS and depression, the latter group showed a significant and severe hypometabolism of the medial and upper frontal regions bilaterally ($P = 0.037–0.001$), whereas the metabolism of brain stem was normal. Brain ^{18}FDG PET showed specific metabolism abnormalities in patients with CFS in comparison with both healthy controls and depressed patients. The most relevant result of our study is the brain stem hypometabolism which, as reported in a perfusion SPECT study, seems to be a marker for the in vivo diagnosis of CFS. *Am J Med.* 1998;105(3A):54S–58S. © 1998 by Excerpta Medica, Inc.

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Chronic fatigue syndrome (CFS) is a debilitating disorder of unknown etiology characterized by unexplained, deep fatigue lasting ≥6 months. The cause of CFS has not been identified, and no specific diagnostic tests are available to date. The first case definition of CFS did not effectively help physicians to distinguish CFS from other types of unexplained fatigue.[1] For this reason, the revised case definition provided additional guidelines to researchers for subgrouping cases of CFS and other types of unexplained prolonged fatigue.[2] Nevertheless CFS is still not recognized as an independent syndrome by most neurologists and psychiatrists, with depression being the most common final diagnosis in patients with genuine CFS.[3] Diagnosis of depression is usually based on the neuropsychological evaluation but, in the CFS setting, it is not easy to distinguish between a primary depressive disorder and a secondary, reactive one. Neurofunctional imaging techniques such as single-photon emission computed tomography (SPECT—to assess perfusion) and positron emission tomography (PET—to assess metabolism) have already been extensively used to study neurologic and psychiatric disorders, especially for differential diagnosis purposes.[4] In a recent review CFS has been included in a group of problematic syndromes in which SPECT may be useful in the differential diagnosis.[5]

We herewith present the results of a study aiming to evaluate brain metabolism of CFS patients, without signs of depression, by using PET and [^{18}F]fluorine-deoxyglucose (^{18}FDG) as tracer. The study was based on a previous experience by perfusion SPECT in a mixed group of CFS, neurologic, and psychiatric disorders that demonstrated a relevant hypoperfusion of brain stem in CFS.[6] As depression is the most frequent neurologic diagnosis in cases of CFS, we examined subjects suffering from major depression, but no other psychiatric patients were included. The aim of our study was to evaluate glucose brain metabolism to assess a possible role of the central nervous system in the pathogenesis of CFS, and to confirm the SPECT perfusion data with the higher resolution of PET, which is able to detect small structures such as brain stem. Patients affected by CFS were evaluated at the Aviano Cancer Center; patients with depression as well as healthy volunteers were evaluated at the Castelfranco

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Table 1. Main Symptoms of Patients With Chronic Fatigue Syndrome

Symptoms	Patients n (%)
Fatigue (according to case definition)	18/18 (100)
Insomnia/hypersomnia	18/18 (100)
Headaches	18/18 (100)
Neuropsychological problems	18/18 (100)
Photophobia or transient scotomata	17/18 (94)
Prolonged periods of low-grade fever	14/18 (78)
Migratory arthralgia	13/18 (72)
Sore throat	13/18 (72)

General Hospital, where PET scans were performed on all patients.

METHODS

In this preliminary study, we enrolled 24 right-handed individuals composed of 18 patients (12 females and 6 males) who fulfilled the Centers for Disease Control and Prevention (CDC) criteria of the working case definition of CFS and 6 patients (4 females and 2 males) affected by major depression according to the DSM-IV-R, and we compared both groups with a group of healthy controls. All patients underwent a complete diagnostic work-up that included history, physical, and neuropsychiatric examination, and brain x-ray computerized tomography (CT) or magnetic resonance imaging (MRI). In all CFS cases, psychiatric diseases were excluded by Brief Psychiatric Rating Scale (BPRS) and Present State Examination (PSE). We also performed Hamilton Rating Scale for Anxiety and 24-item Hamilton Rating Scale for Depression, before PET study, to exclude depression and anxiety neurosis. Mean age was 34 $\pm$ 15 years (range, 15–68) and subjects were drug-naive. Patients affected by major depression were older (mean age 48 $\pm$ 7 years, range 41–59) and the mean duration of the disease was 8 $\pm$ 4 years. They were drug-free for at least 4 weeks before entering the study. Previous head trauma and/or cerebrovascular diseases were excluded for both. Median time from CFS diagnosis was 16 months (range, 9–138). The main symptoms of CFS patients are listed in **Table 1**.

We included a control group comprising 6 age-matched healthy subjects (4 women and 2 men; mean age 38 $\pm$ 12) who were entirely normal on physical examination, with negative history for neurologic and psychiatric diseases. We chose a small group of controls who were composed of a similar percentage of males and females and age-matched with respect to CFS cases. They were young enough to exclude the effect of age, even if this is still controversial, as the findings seen on PET in normal aging are not yet unique.[7–8] All subjects or their relatives gave informed consent to participate in the study.

PET studies were performed using a whole-body, high resolution PET scanner (ECAT EXACT 47 Siemens CTI). This 24-ring bismuth germinate tomograph produces 47 simultaneous slices 3.38 mm thick and the resolution (FWHM) is 6.1 mm along the transaxial plane and 4.8 mm along the axial plane. The correct positioning of the head was assessed by a laser device to define the orbitomeatal line. A transmission scan was performed (10 min acquisition) to obtain the attenuation correction, using orbiting ^{68}Ge rod sources. In resting condition, 210–270 MBq of ^{18}FDG were injected into an antecubital vein with ears unplugged and eyes closed. Emission scan data were acquired 45 min after injection. In controls, depressed patients, and in 10 of 18 CFS subjects, we also obtained the cardiac input functions for calculating regional cerebral metabolic rate for glucose (rCMRgl) following a methodology described in a previous experience.[9] Transaxial, coronal, and sagittal slices were reconstructed from raw data both for qualitative (nonparametric) and quantitative (parametric) studies. On 6-mm thick transaxial slices (about 16 per study) we performed a region of interest (ROI) analysis positioning several anatomical ROIs, based on isocontour techniques, comparing the PET images with a standard brain atlas[10] and outlining the entire region on each image. The ROIs, 50–54 per study, were used to sample the different brain areas of the cortex, basal ganglia, thalamus, cerebellum, and brain stem. At least 3 contiguous slices were used to obtain information from each area by averaging the data from these planes. The resulting 22 cortical and subcortical areas were: (1) left inferior frontal (comprising orbito–frontal region); (2) right inferior frontal; (3) left mediofrontal (comprising mediofrontal gyrus and the lower region of superior frontal gyrus); (4) right mediofrontal; (5) left superior frontal; (6) right superior frontal; (7) left parietal; (8) right parietal; (9) left inferior temporal (comprising hippocampus and mesial cortex); (10) right inferior temporal; (11) left superior temporal (comprising primary auditive cortex); (12) right superior temporal; (13) left occipital cortex (including primary visual cortex); (14) right occipital cortex; (15) left nucleus caudate; (16) right nucleus caudate; (17) left putamen; (18) right putamen; (19) left thalamus; (20) right thalamus; (21) brain stem; and (22) cerebellum (taken as a whole). The same set of ROIs was used for both parametric and nonparametric PET images to obtain the mean values of all areas in rGMRgl and μCi per pixel, respectively. Then, for each study, we computed the mean brain activity (MBA), as mean value of all ROIs, and we normalized each cortical and subcortical area to this mean (e.g., left inferior frontal A = mean value of the ROIs on left inferior frontal cortex/MBA). Group means were compared using the 2-tailed Student's *t* test for unpaired comparisons. The level of statistical significance was set at $P < 0.05$.

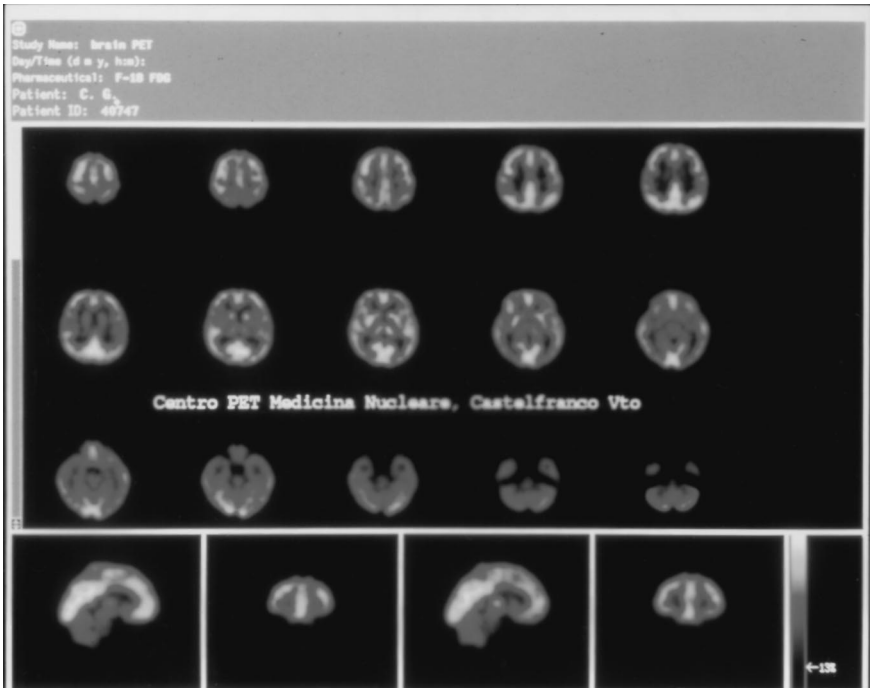

Figure 1. CFS patient: PET transaxial, coronal, and sagittal slices showing the low uptake brain stem.

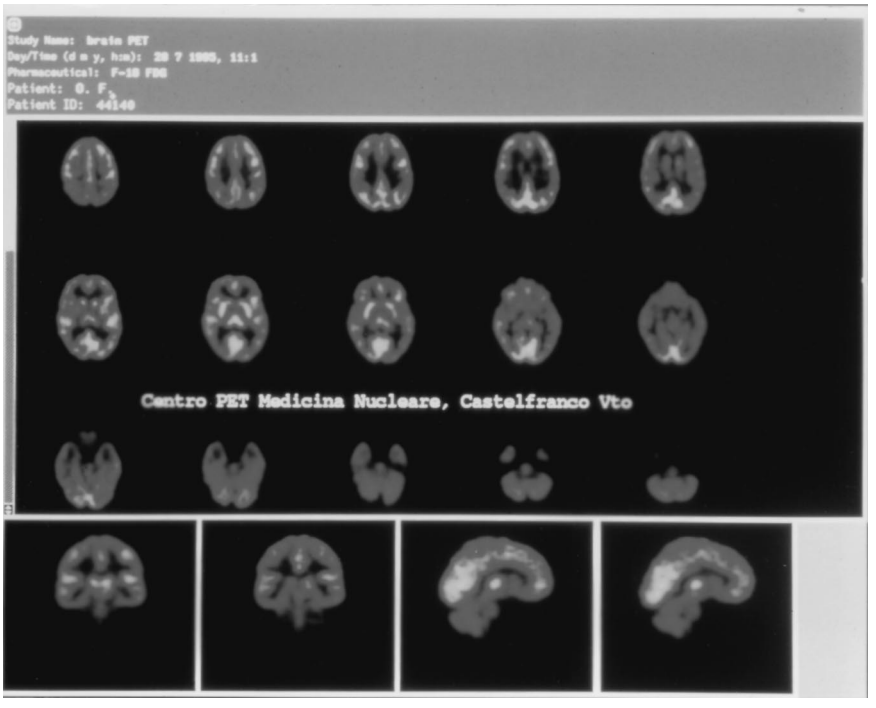

Figure 2. Depressed patient: transaxial, coronal, and sagittal PET images, showing the low frontal and normal brain stem glucose metabolism.

RESULTS

Conventional radiologic imaging (MRI and CT) was normal in both groups of patients showing no focal defects or significant brain atrophy. For visual inspection of PET imaging, the reduction of metabolism was considered to be mild (<10% of the color scale), moderate (10–20%

Table 2. Frontal Cortex–Brain Stem Mean Brain Activity in CFS and Depression

	Depression Mean	SD	CFS Mean	SD	*P* Value
Left inferior frontal	1.00	0.06729	1.03	0.03912	NS
Right inferior frontal	0.96	0.04539	1.02	0.05217	0.037
Left mediofrontal	0.96	0.05148	1.04	0.0453	0.002
Right mediofrontal	0.96	0.05768	1.02	0.03689	0.037
Left superior frontal	0.77	0.048697	1.06	0.04936	0.001
Right superior frontal	0.76	0.048517	1.04	0.04299	0.001
Brain stem	0.77	0.13645	0.65	0.06257	0.009

less), or severe (>20%). CFS patients, with respect to controls, showed moderate hypometabolism of brain stem, especially the pons (**Figure 1**). In depressed subjects, a severely impaired glucose metabolism in frontal areas was evident (**Figure 2**). In CFS, normalized nonparametric PET data revealed a significant hypometabolism of right mediofrontal cortex ($P = 0.010$) and brain stem ($P = 0.013$) compared with healthy subjects. Comparing major depression and CFS, the whole frontal cortex was affected (except the left inferior frontal) with $P = 0.037–0.001$ in the first group of patients, while in CFS patients, the brain stem was severely and significantly hypometabolic ($P = 0.009$; **Table 2**). Absolute, quantitative ^{18}FDG PET data showed normal values for the mean (40 ± 12 μmol/100 g/min) rCMRgl in both depressed and CFS patients. The normalization of parametric images, by using the same set of ROIs as the nonparametric studies, demonstrated the same involvement of previously reported brain areas.

DISCUSSION

To date, no diagnostic tests are available for CFS, which is currently diagnosed by a history of illness suggestive of CFS along with the systematic exclusion of other possible causes of fatigue. Applications and limitations of functional neuroimaging in the diagnosis of CFS have recently been reviewed.[11] MRI and CT are anatomical approaches which, in CFS, yielded conflicting and substantially inconclusive results.[12–13] PET and SPECT offer noninvasive in vivo methods for assessing directly regional brain functions. Regional brain blood flow, oxygen metabolism, and glucose utilization, blood–brain barrier permeability, and presynaptic and postsynaptic neuroreceptor density and affinity are some of the neurophysiologic variables that can be studied by these techniques.[14–16] Several studies have been published using SPECT in CFS, although the results vary across research centers, probably reflecting a different selection of patients. Initial reports of regional SPECT abnormalities involved frontal, parietal, temporal, and occipital areas within a widespread cortical hypoperfusion.[17] The involvement of frontal and temporal regions was successfully described[18] both in depressed and CFS patients, suggesting important similarities, and also raising the question of differential diagnosis between these disorders.

Recently Costa et al[6] compared brain perfusion of patients affected by myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) with that of normal volunteers and other patients with major depression. The results indicated that in addition to scattered cortical perfusion abnormalities, brain stem hypoperfusion (compared with normals) appeared to be characteristic of ME/CFS patients, and it was significantly lower than that of depressed patients. The brain stem hypoperfusion was the lowest in those ME/CFS patients who fulfilled the CDC criteria for CFS and had no other psychiatric disorder.

To describe the PET pattern in CFS patients, and to study PET usefulness in differential diagnosis between CFS and depression, we measured brain metabolism in patients affected by CFS without depression and in patients affected by depression without CFS, comparing both groups of patients with a control group of healthy subjects. Absolute glucose metabolism data and normalized data showed that the brain glucose metabolism is impaired in selected and different areas, in both CFS and depression. In CFS, with respect to healthy subjects, we found a significant hypometabolism of right mediofrontal cortex, in agreement with a previous SPECT study by perfusion tracers.[18] Our group of depressed patients presented more severe and widespread frontal alterations, as already reported in depression[19] and in other psychiatric syndromes, especially schizophrenia, and obsessive-compulsive disorder.[20–25] PET and SPECT studies have not yet identified specific patterns for each disease, but, generally, the frontal alterations are not focal, as we conversely found in our experience with CFS. We can argue that this limited involvement of frontal cortex in CFS may be a feature of the disease. Alternatively, we can consider it as an expression of reactive, not yet clinically evident, depression. Hypothetically, taking into account that in our regional analysis, medium frontal cortex comprised brain areas 9 and 46 (association cortex), this derangement of right hemisphere may explain some neurocognitive impairments of the disease.

More specifically, we found a significant hypometabo-

lism of the brain stem, confirming the report of other investigators (see above); this seems a typical feature of CFS never reported, to our knowledge, in psychiatric diseases. Previous SPECT studies were able to identify such involvement, even if this technique has an anatomical resolution lower than our high resolution PET. To date, this finding has no clear explanation, especially in defining such damage as that primary or secondary to CFS. The brain stem is involved in many functions of vegetative life. Animal models have shown[26] a predilection for the brain stem and diencephalon by some herpes viruses, the Epstein-Barr virus, and herpes virus type 6, which have been often implicated in CFS pathogenesis.[12–27] As already suggested by Costa et al, this virus-mediated brain stem impairment might be the cause rather than the consequence of the disease and might explain some manifestations of CFS by the involvement of the reticular system (i.e., sleep disturbances and consciousness alterations).

In conclusion, although preliminary, our study is in agreement with previous neurofunctional imaging studies supporting an organic cause for CFS. Because of its cost, PET procedure should not be considered appropriate for the clinical diagnosis of CFS. Nonetheless, in the near future, PET could become extremely useful in testing new pathogenetic hypotheses as well as new therapeutic approaches, especially in selected subsets of patients.

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